Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

OBJECTIVE

To determine the benefits and harms of medical cannabis and cannabinoids for chronic pain.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

MEDLINE, EMBASE, AMED, PsycInfo, CENTRAL, CINAHL, PubMed, Web of Science, Cannabis-Med, Epistemonikos, and trial registries up to January 2021.

STUDY SELECTION

Randomised clinical trials of medical cannabis or cannabinoids versus any non-cannabis control for chronic pain at ≥1 month follow-up.

DATA EXTRACTION AND SYNTHESIS

Paired reviewers independently assessed risk of bias and extracted data. We performed random-effects models meta-analyses and used GRADE to assess the certainty of evidence.

RESULTS

A total of 32 trials with 5174 adult patients were included, 29 of which compared medical cannabis or cannabinoids with placebo. Medical cannabis was administered orally (n=30) or topically (n=2). Clinical populations included chronic non-cancer pain (n=28) and cancer related pain (n=4). Length of follow-up ranged from 1 to 5.5 months. Compared with placebo, non-inhaled medical cannabis probably results in a small increase in the proportion of patients experiencing at least the minimally important difference (MID) of 1 cm (on a 10 cm visual analogue scale (VAS)) in pain relief (modelled risk difference (RD) of 10% (95% confidence interval 5% to 15%), based on a weighted mean difference (WMD) of −0.50 cm (95% CI −0.75 to −0.25 cm, moderate certainty)). Medical cannabis taken orally results in a very small improvement in physical functioning (4% modelled RD (0.1% to 8%) for achieving at least the MID of 10 points on the 100-point SF-36 physical functioning scale, WMD of 1.67 points (0.03 to 3.31, high certainty)), and a small improvement in sleep quality (6% modelled RD (2% to 9%) for achieving at least the MID of 1 cm on a 10 cm VAS, WMD of −0.35 cm (−0.55 to −0.14 cm, high certainty)). Medical cannabis taken orally does not improve emotional, role, or social functioning (high certainty). Moderate certainty evidence shows that medical cannabis taken orally probably results in a small increased risk of transient cognitive impairment (RD 2% (0.1% to 6%)), vomiting (RD 3% (0.4% to 6%)), drowsiness (RD 5% (2% to 8%)), impaired attention (RD 3% (1% to 8%)), and nausea (RD 5% (2% to 8%)), but not diarrhoea; while high certainty evidence shows greater increased risk of dizziness (RD 9% (5% to 14%)) for trials with <3 months follow-up versus RD 28% (18% to 43%) for trials with ≥3 months follow-up; interaction test P=0.003; moderate credibility of subgroup effect).

CONCLUSIONS

Moderate to high certainty evidence shows that non-inhaled medical cannabis or cannabinoids results in a small to very small improvement in pain relief, physical functioning, and sleep quality among patients with chronic pain, along with several transient adverse side effects, compared with placebo. The accompanying *BMJ* Rapid Recommendation provides contextualised guidance based on this body of evidence.

SYSTEMATIC REVIEW REGISTRATION

https://osf.io/3pwn2

WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic pain is a common complaint that is increasingly managed with medical cannabis or cannabinoids.

Prior systematic reviews exploring the effectiveness of medical cannabis for chronic pain have provided conflicting results due, in part, to limitations of analytical approaches and interpretation of findings.

WHAT THIS STUDY ADDS

A *BMJ* Rapid Recommendation guideline panel, including patients, clinical experts, and methodologists, defined the scope of our review, informed outcome selection and importance, subgroup analyses, and interpretation of findings.

Moderate to high certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids results in a small to very small increase in the proportion of people living with chronic pain who experience an important improvement in pain relief, physical functioning, and sleep quality.

High certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids does not improve emotional, role, or social functioning.

Moderate to high certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids results in a small increase in the proportion of patients experiencing cognitive impairment, vomiting, drowsiness, dizziness (and large increase at longer follow-up), impaired attention, and nausea, but not diarrhoea.

Introduction

Chronic pain affects approximately 20% of North Americans,[1 2] Europeans,[3 4] Australians,[5] and populations in developing countries,[6] and is associated with physical and emotional impairment, disability, reduced quality of life, and increased healthcare costs.[3-12] The shift away from long term opioid therapy for chronic pain has increased interest in medical cannabis as a therapeutic alternative[13 14]; however, formal guidance has been variable. Some guidelines recommend cannabis for chronic pain only after other treatments have proved unsuccessful,[15] others only for chronic non-cancer pain,[16] chronic neuropathic pain,[15 17] palliative care, or refractory neuropathic pain,[18] while some guidelines recommend against use of medical cannabis for chronic pain.[19 20]

The systematic reviews[15 16 18 19 21-24] supporting these guidelines have several limitations, including exclusion of some types of medical cannabis,[23] consideration of select chronic pain conditions,[16 22] or incomplete search strategies.[16 21 23 24] Other limitations include only pooling reported responder analyses (such as ≥30% or 50% pain reduction from baseline),[16 18 21 24] which excluded the majority of trials that only reported pain as a continuous outcome; using standardised mean differences to pool continuous data,[16 21 22 24] which is vulnerable to baseline heterogeneity of patients and difficult to interpret[25]; failure to explore heterogeneity associated with pooled treatment effects[16 21 23 24]; lack of patient involvement[15 21]; and insufficient evaluation of the certainty of evidence.[15 21 22]

We conducted a systematic review and meta-analysis of randomised clinical trials (RCTs) to evaluate the effectiveness and safety of medical cannabis and cannabinoids for chronic pain that addresses these limitations. This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (https://magicevidence.org) and *The BMJ*. This systematic review informed a parallel guideline published on bmj.com[26] and MAGICapp (box 1).

Methods

We followed the PRISMA statement for reporting systematic reviews of RCTs[27] and registered our review on the Open Science Framework (https://osf.io/3pwn2). Before analysis, we planned a sensitivity analysis comparing reported versus modelled proportion of patients achieving ≥30% pain reduction with medical cannabis. We also conducted a post hoc subgroup analysis to explore the impact of industry funding versus not on treatment effects.

Guidline panel involvement

The *BMJ* Rapid Recommendations guideline panel provided critical oversight of different steps of this review, including: (1) defining the study question; (2) categorising chronic pain conditions; (3) prioritising outcome measures; (4) ranking the importance of adverse events; (5) proposing subgroup analyses; and (6) informing if measures of precision associated with pooled effect estimates were imprecise. The panel included nine content experts (two general internists, two family physicians, a paediatrician, a physiatrist, a paediatric anaesthesiologist, a clinical pharmacologist, and a rheumatologist), nine methodologists (five of whom are also front-line clinicians), and three people living with chronic pain (one of whom used medical cannabis). All patient partners received personal training and support to optimise contributions throughout the guideline development process. The members of the guideline panel led the interpretation of the results based on what they expected the typical values and preferences of patients to be, as well as the variation between patients.

Patient and public involvement

The three patient partners were full members of the guideline panel and contributed to the selection and prioritisation of outcomes, values and preferences assessments, critical feedback to the protocol, and the interpretation of findings for the systematic review and the associated *BMJ* Rapid Recommendation.

Data sources

We searched MEDLINE, EMBASE, AMED, PsycInfo, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, PubMed, Web of Science, Cannabis-Med, and Epistemonikos from inception to 7 February 2020, which formed the basis for evidence used by the guideline panel to formulate recommendations. We updated our search to 15 January 2021 to explore for additional eligible trials. We searched Clinical Trials.gov, WHO International Clinical Trials Registry Platform (ICTRP), EU Clinical Trials Register, and Health Canada Clinical Trials Database in May 2020 and again in January 2021. No language restrictions were applied, and an academic librarian developed all database-specific search strategies (see eAppendix 1 in the data supplement on bmj.com). In addition, we reviewed the reference lists of eligible reports, previous systematic reviews, and guidelines, and contacted industry representatives to identify additional studies.

Eligibility criteria

We included RCTs that enrolled ≥20 chronic pain patients (pain lasting ≥3 months),[28] randomised them to any form of medical cannabis or cannabinoids versus placebo or a non-cannabis active comparator, and followed them for at least one month. We included trials for multiple sclerosis only when enrolled patients were described as presenting with chronic pain[29-34] or baseline data confirmed the presence of chronic pain.[35-38] We excluded conference abstracts, ongoing trials, open-label trials, and studies that enrolled patients without chronic pain or with a total sample size less than 20 patients,[39] as studies with very small samples are more prone to bias (such as unequal distribution of prognostic factors at baseline) and contribute little information to pooled analyses.[40] We contacted authors to clarify eligibility criteria when

Box 1: Linked articles in this *BMJ* Rapid Recommendation cluster

- Busse JW, Vankrunkelsven P, Zeng L, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. *BMJ* 2021;374:n2040. doi:10.1136/bmj.n2040
  - Summary of the results from the Rapid Recommendation process
- Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ* 2021;374:n1034
  - Review of randomised trials that assessed medical cannabis or cannabinoids for chronic pain
- Zeraatkar D, Cooper MA, Agarwal A, et al. Long-term and serious harms of medical cannabis or cannabinoids for chronic pain: a systematic review of non-randomised studies. *medRxiv* 2021 doi:10.1101/2021.05.27.21257921
  - Review of observational studies exploring long term harms associated with use of medical cannabis or cannabinoids for chronic pain
- Zeng L, Lytvyn L, Wang X, et al. Values and preferences towards medical cannabis or cannabinoids among patients with chronic pain: a mixed methods systematic review. *BMJ Open* 2021;0:e050831. doi:10.1136/bmjopen-2021-050831.
  - Review of studies exploring patients' values and preferences regarding use of medical cannabis or cannabinoids for chronic pain.
- Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open* 2021;11:e047717. doi:10.1136/bmjopen-2020-047717
  - Review of evidence assessing the impact of medical cannabis or cannabinoids when added to opioids among patients living with chronic pain.
- MAGICapp (https://app.magicapp.org/#/guideline/jMMYPj)
  - Expanded version of the results with a multilayered recommendation, evidence summaries, and decision aids for use on all electronic devices

necessary and excluded studies if we did not receive a response.

Study selection

Using a standardised pilot-tested form, paired reviewers screened titles and abstracts of identified citations and full texts of potentially eligible studies. Reviewers resolved disagreements by discussion, or with an adjudicator's help when they could not achieve consensus. We used online systematic review software (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.net/) to facilitate literature screening.

Data extraction

Using standardised, pilot-tested forms, each eligible trial underwent duplicate data abstraction by pairs of reviewers working independently. Reviewers addressed discrepancies through discussion or adjudication by a third reviewer when necessary. If a study reported outcomes at several time points, we used the longest follow-up.

We collected information regarding study characteristics, treatment details (such as dose, mode of administration, duration of treatment), patient characteristics (including category of pain condition as guided by the International Association for the Study of Pain[41 42]), and all patient-important outcomes as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials[43 44] (pain, physical functioning, sleep quality, emotional functioning, role functioning, social functioning, and adverse events). Based on feedback from our patient partners, we used pain at rest rather than on movement if both were reported, and we used upper limb function rather than lower limb function if both were reported and overall function was not. If multiple instruments were used to measure the same outcome domain (such as pain), we collected data from the most commonly reported instrument across trials eligible for our review. On review of adverse events reported among eligible trials, our guideline panel selected seven as most important to patients, in the following order of importance: (1) cognitive impairment, (2) vomiting, (3) drowsiness, (4) dizziness, (5) impaired attention, (6) diarrhoea, and (7) nausea.

Risk of bias assessment

Using a modified Cochrane risk of bias instrument,[45 46] pairs of reviewers, independently and in duplicate, assessed each article for risk of bias, including random sequence generation, allocation concealment, blinding of participants, care givers, outcome assessors, outcome adjudicators, and data analysts, and incomplete outcome data (≥20% missing data was considered high risk of bias).

Statistical analysis

We measured inter-rater agreement of the decision to include a trial after reviewing the full-text paper using an adjusted kappa statistic (κ).[47] We converted all continuous measures to a common scale on a domain-by-domain basis[48]: (1) pain intensity to a 10 cm visual analogue scale (VAS), higher scores are worse; (2) physical functioning to the 100-point 36-Item Short Form Survey (SF-36) physical functioning scale, higher scores are better; (3) emotional functioning to the 100-point SF-36 mental functioning scale, higher scores are better; (4) role functioning to the 100-point SF-36 scale of role limitations due to physical problems, higher scores are better; (5) social functioning to the 100-point SF-36 social functioning scale, higher scores are better; and (6) sleep quality to a 10 cm VAS, higher scores are worse. Crossover trials were analysed as parallel trials, thus, total number of patients enrolled were doubled.

We used change scores from baseline rather than end-of-study scores to account for inter-patient variability. If the authors did not report change scores, we calculated them using the baseline and end-of-study score and a correlation coefficient.[49 50] We pooled all continuous outcomes reported by more than one study as the weighted mean difference (WMD) and the associated 95%confidence interval, and modelled the risk difference (RD) of achieving at least the minimally important difference (MID).[50] The MID is the smallest amount of improvement in a treatment outcome that patients recognise as important.[51] For the 10 cm VAS for pain and sleep quality, the MID has been established as approximately 1 cm.[52 53] For the SF-36, a MID of 10 points was used for all individual scales (that is, physical, emotional, role, and social functioning).[54]

Modelling assumptions for estimating the RD of achieving the MID assume that the standard deviations (SDs) of outcome measurements are the same in both the treatment and control groups, and that change scores in both groups are normally distributed.[50] We explored if these assumptions were likely to have been met by comparing SDs between treatment and control groups, and calculating the mean score for pain ±2 SDs in each treatment group for all trials that contributed to our responder analysis to identify any cases in which the distributions were substantially skewed.

We pooled the effect of medical cannabis on adverse events and directly reported pain responder analyses (that is, ≥30% pain relief from baseline, which was the threshold most commonly applied among trials reporting the proportion of responders) as relative risks (RRs), RDs and the associated 95% CIs. We used the DerSimonian-Laird method and random-effects models for all meta-analyses, which are conservative as they consider both within- and between-study variability.[55]

Missing data

If standard errors (SEs) of effect measures or SDs for continuous outcomes were not reported directly, we estimated SEs from confidence intervals or P values, or SDs from SEs, confidence intervals, or P values.[49] When necessary, we estimated the sample mean and SD from sample size, median, interquartile range, or range.[56] We contacted authors to acquire missing SEs or SDs when there were no variance-related information reported. If unsuccessful, we imputed missing SEs using the hot deck approach[50] or missing SDs by assuming a linear relationship between SDs and means among other studies reporting this information and contributing to the pooled effect.[49]

Some authors reported the effect of medical cannabis was not statistically significant, but without accompanying data. If we were unable to acquire these data by contacting the author, we addressed the risk of overestimating the magnitude of association by imputing a WMD of "0" or RR of "1" for effect estimates and imputed the associated variance using the hot deck approach.[50]

Subgroup analyses, sensitivity analyses, and meta-regression

We used the Cochran's χ^2 test and the I^2 statistic to examine statistical heterogeneity of pooled effect estimates.[49] In consultation with the guideline panel, we tested the following a priori subgroup hypotheses that larger treatment effects were associated with: (1) chronic non-cancer pain versus chronic cancer related pain; (2) neuropathic pain versus non-neuropathic pain; (3) tetrahydrocannabinol (THC) alone versus THC and cannabidiol (CBD) versus CBD alone versus palmitoylethanolamide (PEA); (4) inhaled versus ingested versus topical cannabis; (5) enriched enrolment versus not; (6) high versus low risk of bias on a component-by-component basis; and (7) industry funded trials versus not. We conducted subgroup analyses only if there were two or more studies in each subgroup.

We used meta-regression to explore the association between treatment effects and length of follow-up and the proportion of loss to follow-up when there were at least 10 studies available.[49 57] We assessed the credibility of subgroup effects using ICEMAN criteria.[58] We conducted sensitivity analyses excluding converted change scores, and excluding data imputation for non-significant effects, to explore the impact on pooled effect estimates. Among trials that directly reported the proportion of patients achieving ≥30% pain reduction from baseline (which equated to approximately a 2 cm reduction in pain on a 10 cm VAS), we calculated both the responder analysis and a modelled responder analysis of achieving ≥2 cm pain reduction to explore consistency of results. We also pooled effect estimates with the Hartung-Knapp-Sidik-Jonkman method as a sensitivity analysis.[59]

Small study effects

When there were at least 10 studies available for meta-analysis,[49] we assessed for small study effects by visual assessment of asymmetry of the funnel plot for each outcome and calculated Egger's test[60] for continuous outcomes and Harbord's test[61] for binary outcomes.

Certainty of evidence

The authors and the guideline panel achieved consensus in categorising the certainty of evidence for all reported outcomes as high, moderate, low, or very low using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[62] If subgroup analysis showed a significant difference in treatment effect between trials at low and high risk of bias (on a component-by-component basis), we presented the pooled effect for studies at low risk of bias. If no significant subgroup effect was found, we pooled across all trials and did not rate down for risk of bias. Rating of imprecision was fully contextualised by the guideline panel. We also rated down significant effects for imprecision if they were informed by <300 patients for continuous outcomes or <300 events for dichotomised outcomes.[63] We did not rate down the same effect estimate twice for both inconsistency and imprecision. We followed GRADE guidance for communicating our findings.[64]

We performed all statistical analyses using Stata statistical software version 15.1 (StataCorp, College Station, TX, USA). All comparisons were 2-tailed using a threshold of P ≤0.05.

Results

Of 11 952 citations, 31 English language trials[29-38 65-85] and one German language trial[86] met eligibility criteria, including one article[80] that reported two trials and two articles[36 37] that reported outcomes at different follow-up times for the same trial. Thus, we included 32 unique trials with 5174 patients (fig 1). We shared our list of eligible trials with representatives from Canopy Growth, CannaPiece, the Cronos Group, Dosist,

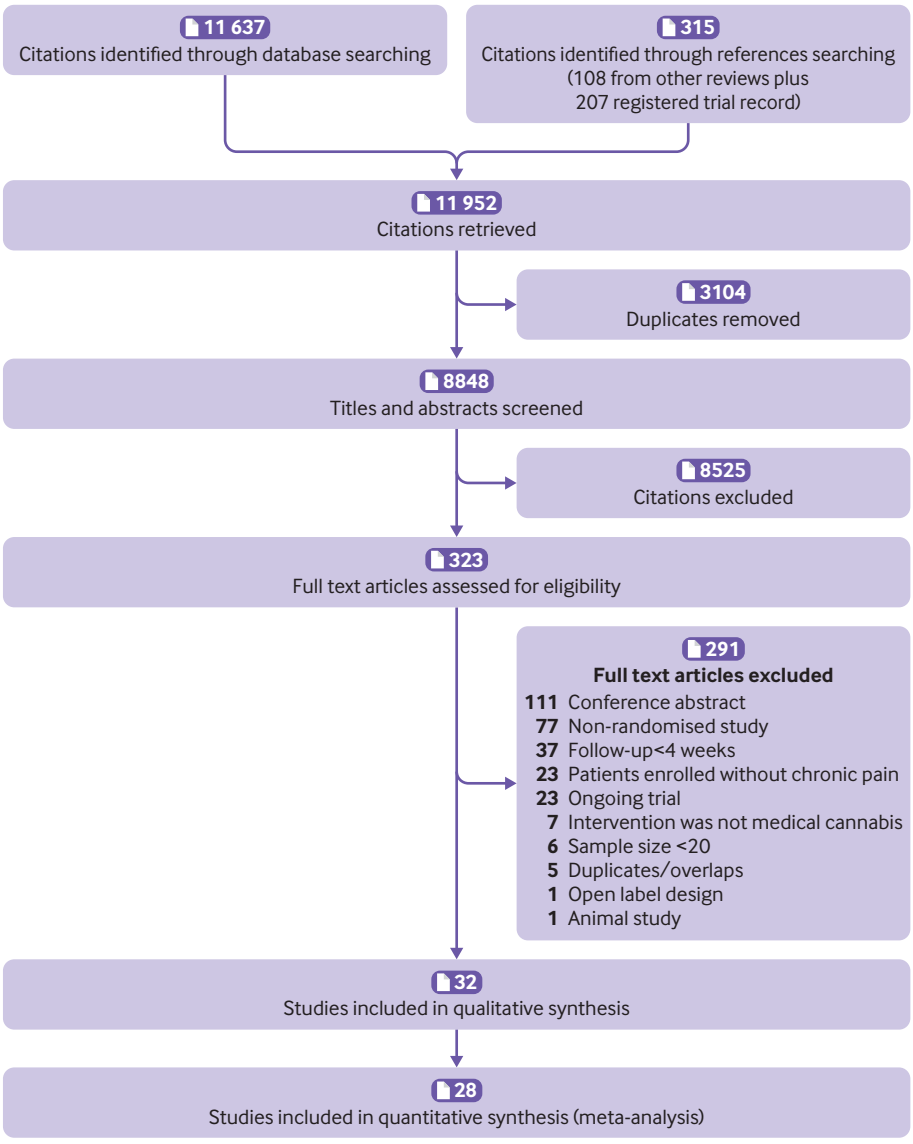


Fig 1 | Studies included in review of medical cannabis or cannabinoids for people living with chronic pain

Tilray, Whistler Therapeutics, Tetra Bio-Pharma, Syqe Medical, the Organic Green Dutchman, International Cannabis Solutions, and Harvest Medical; seven representatives replied and indicated they were unaware of any trials missing from our review. One trial (n=34) of cannabidivarin versus placebo for HIV associated neuropathic pain (information summarised in eTable 1 in data supplement) was identified after guideline recommendations were made. We did not include the results of this trial in our pooled estimates of treatment effects to maintain consistency with the evidence used by the guideline panel to formulate recommendations.

Studies excluded due to short follow-up (<4 weeks), small sample size (<20 patients), or open-label design, as well as ongoing trials, are reported in eAppendix 2. There was almost perfect agreement between reviewers at the full text review stage (κ=0.81). Of 14 authors contacted for clarification of eligibility,[35 87-99] three responded.[92 94 99] Of 13 authors contacted for additional information,[31 66 68 75-79 85 100-103] five provided data.[75 76 78 85 103]

Study characteristics

Among eligible trials, 28 enrolled patients living with chronic non-cancer pain and four enrolled patients with chronic cancer related pain.[79-81] Types of chronic non-cancer pain included neuropathic pain (n=11 trials), spasticity related pain (n=7), nociplastic pain (n=5), nociceptive pain (n=2), medication overuse headache (n=1), and mixed chronic non-cancer pain (n=2) (eTable 2). Among 21 trials that reported baseline pain,[29-31 33 65 66 68 69 71 73-76 79-83 85 86] the mean baseline pain score was 6.10 cm on a 10 cm VAS (median of individual trials 6.28, interquartile range (IQR) 5.67-6.73 cm). The median of the mean age among eligible trials was 53 years (IQR 50-60 years); among 31 trials reporting sex distribution, 55% (2715/4955) of enrolled patients were female (median of individual trials 60%, IQR 39-70%).

Placebo was the most common control (29 of 32 trials), including one three-arm trial that compared palmitoylethanolamide (PEA) with placebo and celecoxib[66]; other active comparators included dihydrocodeine,[67] ibuprofen,[70] and saw palmetto.[77] Topical cannabidiol (CBD) was administrated in two trials[78 83] (including one two-dose CBD versus placebo trial[78]) and oral cannabidivarin (CBDV; a homologue of CBD) in one trial,[85] PEA in five trials,[66 68 76 77 82] tetrahydrocannabinol (THC) in nine trials,[31 33 34 67 70 73-75 86] a combination of THC and CBD in 14 trials[29 30 32 35 38 65 69 71 72 79 80 81 84] (including one three-dose THC-CBD versus placebo trial[79]), and one three-arm trial reported in two articles that compared THC, THC-CBD, and placebo.[36 37] Sixteen trials administered cannabis as gel filled capsules or oil drops,[31-34 36 66-68 70 73-77 85 86] 13 as an oral spray,[29 30 35 38 65 69 71 72 79-81 84] one as sublingual oil drops,[82] and two as a transdermal cream.[78 83] No trial of inhaled medical cannabis (smoked or vapourised) was eligible because of inadequate length of follow-up (<4 weeks). Non-inhaled medical cannabis was added to patient's pre-trial analgesic therapy in 24 trials,[29-32 34-36 38 67 69-76 79-82 84 86] four trials allowed restricted co-analgesics,[33 65 66 78] one trial did not permit participants to receive additional analgesic therapy,[68] and three were unclear regarding concurrent analgesic therapy.[77 83 85]

The median follow-up was 50 days (IQR 35-84; range 28-154 days). Most trials (21/32, 66%) were funded by industry, six (19%) were not, and five (16%) did not specify a source of funding. Four trials used an enrichment design,[35 38 74 80] in which patients were excluded if there was no improvement and/or intolerable adverse events during an open-label run-in period. No trials reported enrolling veterans, individuals receiving disability benefits, involved in litigation, or presenting with comorbid mental illness. One trial (3%) excluded patients with ongoing litigation associated with their chronic pain.[67] Twenty one trials (66%) excluded patients with current or prior substance use disorder,[29 30 33-35 38 65 67 69 70 72-75 80-85] and 23 trials (72%) excluded patients with mental illness or using psychotropic medication.[29 30 32 33 35 36 38 65 67 69 70 72-75 79-85]

Risk of bias

Among 32 eligible trials, 29 (94%) were at risk of bias for at least one domain, 20 (63%) adequately generated their randomisation sequence, 31 (97%) appropriately concealed allocation, 32 (100%) blinded patients, 31 (97%) blinded care givers, data collectors, and outcome assessors, and four (13%) included a blinded data analyst. Fourteen of 30 trials (47%) reported ≥20% missing outcome data; two trials[68 77] did not report the proportion of missing data (eTable 3).

Outcomes for non-inhaled medical cannabis or cannabinoids versus placebo

Pain relief

Moderate certainty evidence from 27 RCTs (3939 patients)[29-35 38 65 66 68 69 71-76 78-84 86] shows that, compared with placebo, non-inhaled medical cannabis probably results in a small increase in the proportion of patients experiencing pain relief at or above the MID: 10% modelled risk difference (95% CI 5% to 15%) for achieving at least the MID of 1 cm, based on a weighted mean difference (WMD) of −0.50 cm on a 10 cm VAS (95% CI −0.75 to −0.25 cm; fig 2, table 1). There are no subgroup differences in pain relief based on neuropathic versus non-neuropathic pain (test of interaction P=0.21, eFigure 1 in data supplement) or chronic non-cancer versus chronic cancer-related pain (test of interaction P=0.16, fig 2, eTable 4, eAppendix 3). Meta-regression shows a significant association between higher loss to follow-up and less pain relief (P=0.008, eFigure 2); however, this subgroup effect is of very low credibility (eAppendix 3).

Moderate certainty evidence from 10 studies (1691 patients)[29-38 65-84 86 101] that directly reported a responder analysis shows that non-inhaled medical cannabis probably results in a higher proportion of patients experiencing ≥30% pain reduction with medical cannabis versus placebo (relative risk (RR) 1.21, 95% CI 1.004 to 1.47; RD 7%, 0.1% to 16%, eFigure 3, table 1). Our modelled responder analysis for ≥30% pain reduction among these same 10 trials finds the identical RD, but with a more precise estimate of effect (modelled RD 7%, 2% to 12%; eTable 5).

Physical functioning

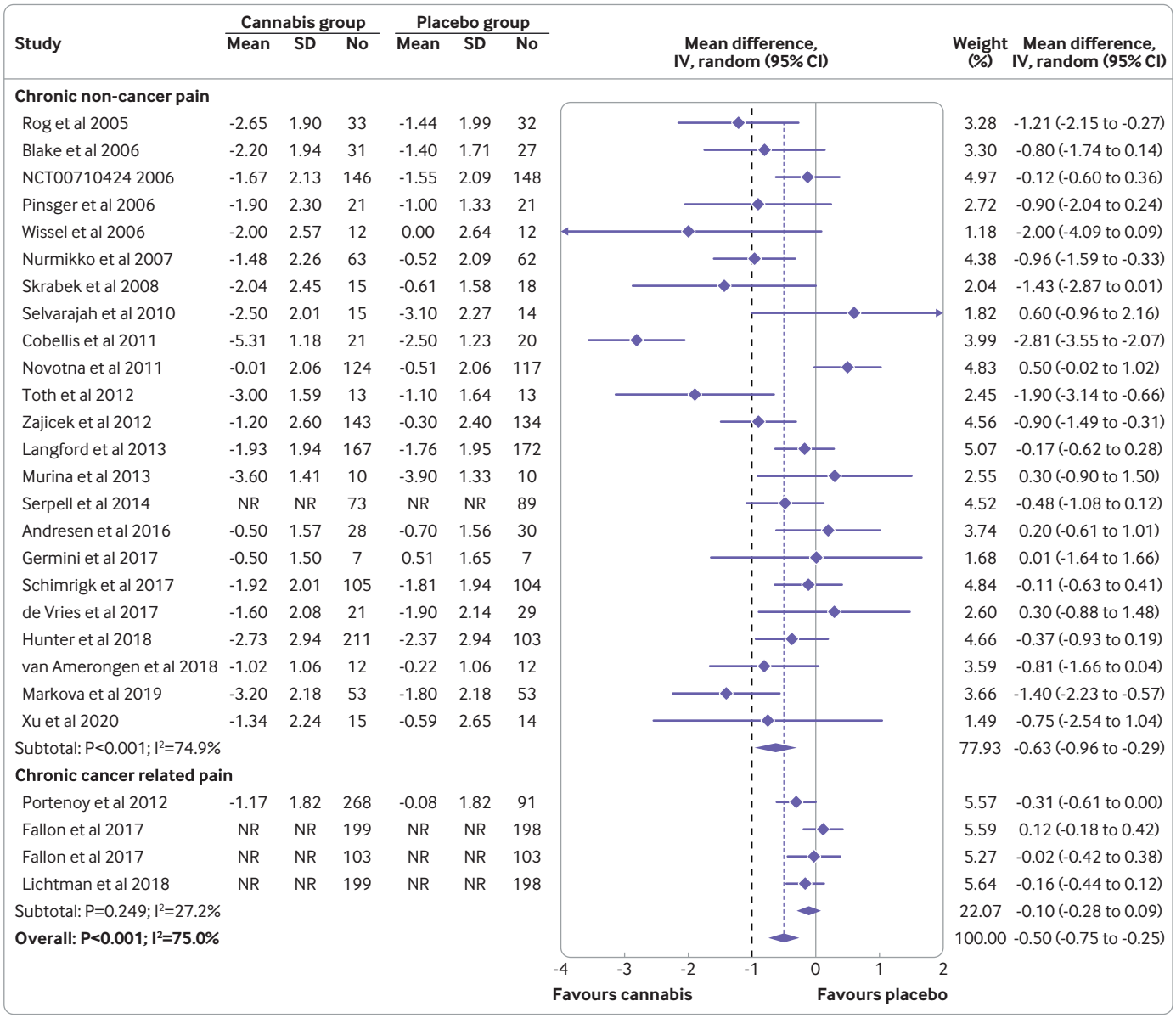
High certainty evidence from 15 RCTs (2425 patients)[29-33 35 36 65 69 71 75 76 79 86] shows that, compared with placebo, medical cannabis taken orally results in a very small increase in the proportion of patients experiencing an improvement of physical functioning at or above the MID: 4% modelled RD (95% CI 0.1% to 8%) for achieving at least the MID of 10 points, based on a WMD of 1.67 points on the 100-point SF-36 physical functioning scale (95% CI 0.03 to 3.31; fig 3, table 1).

Sleep quality

Sixteen RCTs (3124 patients)[29 30 32 34 35 38 65 69 72 74 79-82 84] reported sleep quality. Compared with placebo, medical cannabis taken orally probably results in a significant improvement in sleep quality (WMD −0.53 cm on a 10 cm VAS, 95% CI −0.75 to −0.30 cm; eFigure 4); however, we found evidence of small study effects (eFigure 5; Egger's test P=0.02). When restricted to larger trials (standard error of the WMD ≤0.4; Egger's test P=0.24), high certainty evidence from nine RCTs[29 32 35 72 79-81 84] (2652 patients) shows that, compared with placebo, medical cannabis taken orally results in a small increase in the proportion of patients experiencing an improvement of sleep quality at or above the MID: 6% modelled RD (95% CI 2% to 9%) for achieving at least the MID of 1 cm, based on a WMD −0.35 cm on a 10 cm VAS (−0.55 to −0.14 cm; fig 4, table 1).

Emotional functioning

High certainty evidence from 10 RCTs (2115 patients)[29 32-36 71 75 79 86] shows medical cannabis taken orally does not improve emotional functioning compared with placebo (WMD 0.53 points on the



IV = inverse variance; random = random-effects model; NR = arm-level data not reported

Fig 2 | Pain relief on a 10 cm visual analogue scale (VAS) among people living with chronic pain who received non-inhaled medical cannabis or cannabinoids versus placebo. Test of interaction P=0.16 for chronic non-cancer pain versus chronic cancer related pain. Black dashed vertical line represents the minimally important difference of 1 cm for the 10 cm VAS for pain. Purple dashed vertical line represents the overall pooled measure of effect.

100-point SF-36 mental functioning scale, 95% CI −0.67 to 1.73; eFigure 6, table 1).

Role functioning

High certainty evidence from seven RCTs (1128 patients)[29 35 71 75 79 82 86] finds no effect of oral administration of medical cannabis on role functioning compared with placebo (WMD 0.20 points on the 100-point SF-36 role limitations due to physical functioning scale, 95% CI −3.02 to 3.42; eFigure 7, table 1).

Social functioning

High certainty evidence from eight RCTs (1405 patients)[29 32 35 71 75 79 82 86] shows that, compared with placebo, medical cannabis taken orally does not affect social functioning (WMD −0.63 points on the 100-point SF-36 social functioning scale, 95% CI −2.27 to 1.02; eFigure 8, table 1).

Adverse events

One study, which compared topical CBD cream versus placebo for peripheral neuropathy, reported no adverse events during the study period.[83] Another study, which compared two doses of topical CBD cream versus placebo for nociceptive pain (chronic knee pain due to osteoarthritis), reported no difference in dizziness (RR 3.45, 95% CI 0.18 to 66.22).[78]

Moderate certainty evidence shows that medical cannabis taken orally, compared with placebo,

Table 1 | GRADE evidence profile of non-inhaled medical cannabis versus placebo for people living with chronic pain

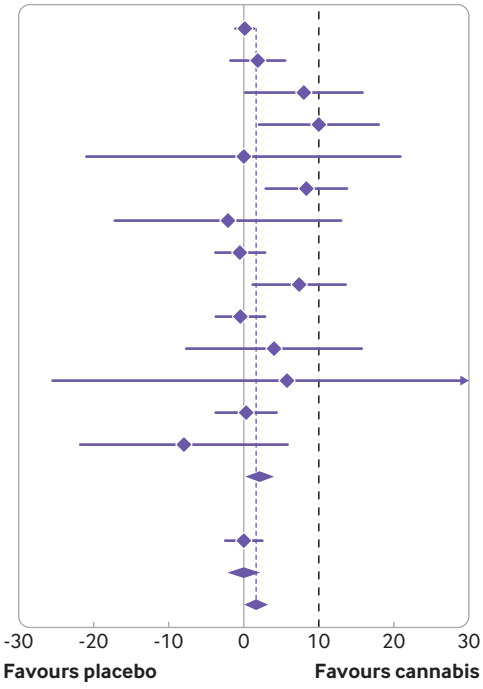
No of trials (No of patients)	Follow-up period (months)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
							Placebo	Cannabis/ cannabinoids	
Pain: 10 cm VAS for pain; lower is better; MID=1 cm									
27 (3939)	1 to 4	No serious risk of bias*	Serious inconsistency I^2=75%	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test P=0.55	952 (52%) achieved at or above MID	1309 (62%) achieved at or above MID	Moderate
							Modelled RD 10% (5% to 15%)		
							WMD −0.50 cm (−0.75 to −0.25)		
Pain: ≥30% pain reduction from baseline									
10 (1691)	1.25 to 3.5	No serious risk of bias*	No serious inconsistency I^2=38%	No serious indirectness	Serious imprecision†	Undetected; Symmetric funnel plot; Harbord's test P=0.77	238 (33%) achieved at or above MID	718 (40%) achieved at or above MID	Moderate
							RD 7% (0.1% to 16%) RR 1.21 (1.004 to 1.47)		
Physical functioning: 0-100 point SF-36 physical functioning scale; higher is better; MID=10 points									
15 (2425)	1 to 4	No serious risk of bias*	No serious inconsistency I^2=46%	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test P=0.10	289 (28%) achieved at or above MID	440 (32%) achieved at or above MID	High
							Modelled RD 4% (0.1% to 8%)		
							WMD 1.67 points (0.03 to 3.31)		
Sleep quality: 0-10 sleep quality scale; higher is worse; MID=1									
9‡ (2652)	1.25 to 3.5	No serious risk of bias*	No serious inconsistency I^2=47%	No serious indirectness	No serious imprecision	Undetected; Symmetric funnel plot; Begg's test P=0.24	601 (48%) achieved at or above MID	765 (54%) achieved at or above MID	High
							Modelled RD 6% (2% to 9%)		
							WMD −0.35 cm (−0.55 to −0.14)		
Emotional functioning: 0-100 point SF-36 mental component summary scale; higher is better; MID=10 points									
10 (2115)	1 to 4	No serious risk of bias*	No serious inconsistency I^2=0%	No serious indirectness	No serious imprecision§	Undetected; Symmetric funnel plot; Begg's test P=0.64	276 (31%) achieved at or above MID	403 (33%) achieved at or above MID	High
							Modelled RD 2% (−2% to 4%)		
							WMD 0.53 points (−0.67 to 1.73)		
Role functioning: 0-100 point SF-36 physical role functioning scale; higher is better; MID=10 points									
7 (1128)	1 to 3.5	No serious risk of bias*	No serious inconsistency I^2=21%	No serious indirectness	No serious imprecision§	Undetected	195 (41%) achieved at or above MID	267 (41%) achieved at or above MID	High
							Modelled RD 0% (−4% to 5%)		
							WMD 0.20 points (−3.02 to 3.42)		
Social functioning: 0-100 point SF-36 social role functioning scale; higher is better; MID=10 points									
8 (1405)	1 to 3.5	No serious risk of bias*	No serious inconsistency I^2=0%	No serious indirectness	No serious imprecision§	Undetected	239 (39%) achieved at or above MID	301 (38%) achieved at or above MID	High
							Modelled RD −1% (−4% to 2%)		
							WMD −0.63 points (−2.27 to 1.02)		
Cognitive impairment									
5 for oral cannabis (1033)	1.25 to 3.5	No serious risk of bias	No serious inconsistency I^2=0%	No serious indirectness	Serious imprecision†	Undetected	7 (1%) experienced cognitive impairment	21 (3%) experienced cognitive impairment	Moderate
							RD 2% (0.1% to 6%)		
							RR 2.39 (1.06 to 5.38)		

95%CI=95% confidence interval; VAS=visual analogue scale; MID=minimally important difference; RD=risk difference; WMD=weighted mean difference; RR=relative risk; SE=standard error.
*We did not rate down for risk of bias as subgroup analysis showed no significant difference in trials at low versus high risk of bias on a component-by-component basis.
†Although the estimate of precision excluded no effect, we rated down for imprecision because the guideline panel determined the lower and upper limits of 95%CI associated with the risk difference included both patient important and unimportant effects, and/or there were less than 300 observations or events to inform the pooled effect estimate.
‡We found evidence of small study effects for sleep quality among 16 eligible studies (Egger's P=0.02). We therefore removed small studies (sample size <130 patients and SE >0.4) from our pooled estimate of effect.
§Although the estimate of precision included no effect, we did not rate down for imprecision because the guideline panel determined that the 95%CI did not include patient-important effects.

probably results in a small increase in the proportion of patients experiencing transient cognitive impairment (five RCTs and 1033 patients; RR 2.39, 1.06 to 5.38; RD 2%, 0.1% to 6%; eFigure 9, table 1), vomiting (9 RCTs and 2284 patients; RR 1.46, 1.07 to 1.99; RD 3%, 0.4% to 6%), drowsiness (15 RCTs and 2505 patients; RR 2.14, 1.55 to 2.95; RD 5%, 2% to 8%), impaired attention (7 RCTs and 895 patients, RR 4.04, 1.67 to 9.74; RD 3%, 1% to 8%), and nausea (14 RCTs and 2877 patients, RR 1.59, 1.28 to 1.99; RD 5%, 2% to 8%); there was no effect on diarrhoea (10 RCTs and 2605 patients; RR 1.53, 0.97 to 2.40) (eTable 6).

Meta-regression shows oral administration of medical cannabis increases the risk of dizziness significantly over time (P=0.03; eFigure 10), and we found evidence of small study effects for trials reporting dizziness with <3 months' follow-up (Harbord's test P=0.03; eFigure 11). Thus, we restricted our analysis to larger trials (standard error of log RR <0.9) for

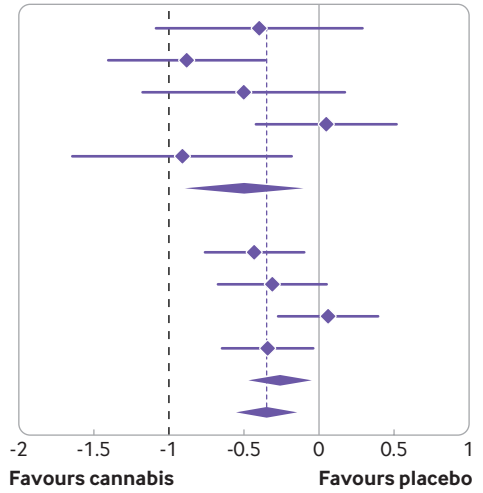
Study	Cannabis group Mean	SD	No	Placebo group Mean	SD	No	Mean difference, IV, random (95% CI)	Weight (%)	Mean difference, IV, random (95% CI)
Chronic non-cancer pain									
Zajicek et al 2003	0.06	6.31	345	-0.04	6.78	183		18.79	0.10 (-1.09 to 1.29)
Rog et al 2005	2.67	7.50	33	0.83	7.33	32		10.38	1.83 (-1.77 to 5.44)
Blake et al 2006	9.00	14.78	31	1.00	15.44	27		3.64	8.00 (0.19 to 15.81)
Pinsger et al 2006	10.00	14.80	21	0.00	11.10	21		3.56	10.00 (2.09 to 17.91)
Wissel et al 2006	NR	NR	12	NR	NR	12		0.59	0.00 (-20.97 to 20.97)
Nurmikko et al 2007	8.01	15.34	63	-0.34	15.34	62		6.43	8.36 (2.98 to 13.74)
Selvarajah et al 2010	3.60	15.26	15	5.70	24.69	14		1.12	-2.10 (-17.16 to 12.96)
Novotna et al 2011	0.30	12.88	124	0.76	12.88	117		11.45	-0.46 (-3.71 to 2.79)
Zajicek et al 2012	37.63	29.00	143	30.25	23.13	134		5.29	7.38 (1.22 to 13.53)
Langford et al 2013	1.56	15.17	167	2.02	15.17	172		11.52	-0.45 (-3.68 to 2.78)
Andresen et al 2016	3.70	24.04	34	-0.30	25.43	34		1.78	4.00 (-7.76 to 15.76)
Germini et al 2017	39.00	22.75	6	33.25	31.75	6		0.27	5.75 (-25.50 to 37.00)
Schimrigk et al 2017	3.50	14.07	105	3.18	15.51	104		9.27	0.32 (-3.69 to 4.33)
de Vries et al 2017	-4.68	23.22	21	3.27	25.94	28		1.32	-7.95 (-21.77 to 5.87)
Subtotal: P=0.021; I^2=48.7%								85.41	2.11 (0.17 to 4.05)
Chronic cancer related pain									
Portenoy et al 2012	NR	NR	268	NR	NR	91		14.59	0.00 (-2.35 to 2.35)
Subtotal: P= ; I^2= %									0.00 (-2.35 to 2.35)
Overall: P=0.028; I^2=45.6%								100.00	1.67 (0.03 to 3.31)



IV = inverse variance; random = random-effects model; NR = arm-level data not reported

Fig 3 | Physical functioning assessed by the 100-point SF-36 physical functioning scale among people living with chronic pain who received non-inhaled medical cannabis or cannabinoids versus placebo. Black dashed vertical line represents the minimally important difference of 10 points for the 100-point SF-36 physical functioning scale. Purple dashed vertical line represents the overall pooled measure of effect.

Study	Cannabis group Mean	SD	No	Placebo group Mean	SD	No	Mean difference, IV, random (95% CI)	Weight (%)	Mean difference, IV, random (95% CI)
Chronic non-cancer pain									
NCT00710424 2006	-2.00	3.02	132	-1.60	2.76	142		6.50	-0.40 (-1.09 to 0.29)
Novotna et al 2011	-0.13	2.05	124	0.75	2.05	117		9.56	-0.88 (-1.40 to -0.36)
Zajicek et al 2012	-1.40	3.10	143	-0.90	2.60	134		6.70	-0.50 (-1.17 to 0.17)
Langford et al 2013	-1.96	2.18	167	-2.00	2.18	172		10.87	0.05 (-0.41 to 0.51)
Serpell et al 2014	-1.49	2.34	73	-0.58	2.34	89		5.99	-0.91 (-1.63 to -0.19)
Subtotal: P=0.069; I^2=53.9%								39.61	-0.50 (-0.90 to -0.11)
Chronic cancer related pain									
Portenoy et al 2012	NR	NR	268	NR	NR	91		15.12	-0.43 (-0.76 to -0.10)
Fallon et al 2017	NR	NR	103	NR	NR	103		14.06	-0.31 (-0.67 to 0.05)
Fallon et al 2017	NR	NR	199	NR	NR	198		14.95	0.06 (-0.27 to 0.39)
Lichtman et al 2018	NR	NR	199	NR	NR	198		16.26	-0.34 (-0.64 to -0.04)
Subtotal: P=0.182 ; I^2=38.2%								60.39	-0.26 (-0.47 to -0.05)
Overall: P=0.056; I^2=47.3%								100.00	-0.35 (-0.55 to -0.14)



IV = inverse variance; random = random-effects model; NR = arm-level data not reported

Fig 4 | Sleep quality on a 10 cm visual analogue scale (VAS) among people living with chronic pain who received non-inhaled medical cannabis or cannabinoids versus placebo Test of interaction P=0.32 for chronic non-cancer pain versus chronic cancer related pain when analysis was restricted to larger trials (standard error of the WMD ≤0.4) due to small study effects. Black dashed vertical line represents the minimally important difference of 1 cm for the 10 cm VAS for sleep quality. Purple dashed vertical line represents the overall pooled measure of effect.

dizziness at <3 months' follow-up. Subgroup analysis of high certainty evidence found oral administration of medical cannabis is associated with higher risk of dizziness at ≥3 months versus <3months (7 RCTs and 2270 patients; RR 4.65, 3.30 to 6.55; RD 28%, 18% to 43%; versus 7 RCTs and 1432 patients; RR 1.95, 1.50 to 2.55; RD 9%, 5% to 14%; test of interaction P=0.003, eFigure 12; moderate credibility of subgroup effect, eAppendix 3).

Outcomes for non-inhaled medical cannabis or cannabinoids versus active comparators

Medical cannabis or cannabinoids versus non-steroidal anti-inflammatory drugs (NSAIDs)

Two trials compared medical cannabis with NSAIDs and reported conflicting results for pain relief.[66 70] One trial, including 41 patients, suggested that PEA was inferior to celecoxib for pain relief among women with nociplastic pain (chronic pelvic pain) (mean difference (MD) 0.91 cm on 10 cm VAS, 95% CI 0.65 to 1.57 cm, low certainty).[66] The other, a crossover trial including 26 patients, suggested there was no significant difference in pain relief for medication overuse headache between THC and ibuprofen (MD −0.90 cm on 10 cm VAS for pain, −1.91 to 0.11 cm, very low certainty).[70] (eTable 7)

Low certainty evidence from the crossover trial including 26 patients with medication overuse headache[70] suggested no difference between THC and ibuprofen on physical functioning (MD 2.30 points on 100 point SF-36 physical functioning scale, 95%CI −1.85 to 6.45), emotional functioning (MD 1.40 points on the 100-point SF-36 mental functioning scale, 95% CI −4.21 to 7.01), vomiting (RR 5.00, 0.25 to 99.34), dizziness (RR 5.00, 0.25 to 99.34), impaired attention (RR 0.33, 0.01 to 7.82), or nausea (RR 0.50, 0.05 to 5.18); no patients in either treatment group reported cognitive impairment or drowsiness (eTable 7).

Medical cannabis or cannabinoids versus opioids

Low certainty evidence from one crossover trial[67] including 73 patients with chronic neuropathic pain suggested nabilone might result in no difference in pain relief compared with dihydrocodeine (MD −0.13 cm on 10 cm VAS for pain, −1.04 to 0.77 cm), physical functioning (MD −1.2 points on 100-point SF-36 physical functioning scale, −4.5 to 2.1 points), emotional functioning (MD 2.5 points on 100-point SF-36 mental functioning scale, −2.7 to 7.6 points), or social functioning (MD 3.4 points on 100-point SF-36 social functioning scale, −4.1 to 10.8 points); but a significant improvement in role functioning (MD 8.9 points on 100-point SF-36 role limitations due to physical functioning scale, 1.1 to 16.7 points) (eTable 8).

Medical cannabis or cannabinoids versus saw palmetto

Low to very low certainty evidence from one trial[77] including 44 patients with nociplastic pain (chronic prostatitis or chronic pelvic pain syndrome) found that, compared with saw palmetto, PEA might improve symptoms (MD −6.00 on International Prostate Symptom Score, 95% CI −9.88 to −2.12) but not erectile function (MD 3.00 on International Index of Erectile Function questionnaire, −0.06 to 6.06) (eTable 9). No significant drug related side effects were observed in either treatment arm.[77]

Additional subgroup analyses, meta-regression, and sensitivity analysis

Among 29 trials comparing non-inhaled medical cannabis with placebo, four trials used fixed doses of PEA[66 68 76 82] and two used topical CBD cream,[78 83] 23 trials (79%) allowed for post-randomisation titration of cannabis dose, which precluded between-trial subgroup analysis of higher versus lower doses of medical cannabis. Two trials compared different doses of medical cannabis with placebo, and no significant dose-response relationship was found for pain relief, physical function, or sleep quality; higher doses of medicinal cannabis containing THC (but not CBD alone) was associated with higher risk of adverse events (eTable 10).[78 79]

No additional subgroup analysis or meta-regression were significant aside from those reported above (eTables 11 to 15). Our sensitivity analyses found no important differences in results whether we incorporated data imputed for non-significant effects. When we excluded change scores converted from baseline and end-of-study scores and used only reported change scores, the effect of non-inhaled medical cannabis on physical functioning became non-significant. Use of the Hartung-Knapp-Sidik-Jonkman method for pooling versus the DerSimonian-Laird method rendered the effect of non-inhaled medical cannabis on physical function and cognitive impairment non-significant (eTables 16 and 17). Most trials (25 of 28, 89%) in which authors provided a measure of variance for pain reported mean effect scores with an associated SD or SE, or MD and 95% CI (eTable 18), suggesting trial authors concluded their data met normal distribution assumptions. When we calculated the mean score for pain ±2 SDs in each treatment group for all trials that contributed to our responder analysis, we found no case in which the results exceeded the range of the study's pain instrument, providing support that distributions were not substantially skewed. Moreover, SDs between treatment and control groups proved very similar (eTable 18).

Discussions

Main findings

Moderate to high certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids results in a small to very small increase in the proportion of patients living with chronic cancer and non-cancer pain who experience an important improvement in pain relief, physical functioning, and sleep quality, along with several adverse side effects. The accompanying *BMJ* Rapid Recommendation

provides contextualised guidance based on this body of evidence.

Our results were restricted to 1-5.5 months' treatment, and most trials explored oral formulations of tetrahydrocannabinol alone or in combination with cannabidiol among adult patients living with chronic pain. Our findings may or may not apply to inhaled forms of medical cannabis, veterans, individuals with substance use disorder or other mental illness, or those involved in litigation or receiving disability benefits.

Relation to other studies

The systematic review of medical cannabis or cannabinoids for chronic pain[23] that informed a 2019 NICE guideline[19] included only 12 of the 31 trials in our review, and included eight additional trials that we excluded because of short follow-up (from 3 hours to 3 weeks),[94 104-108] fewer than 20 patients,[109] or enrolment of patients without chronic pain.[110] Only effects of medical cannabis on pain, physical function, analgesic consumption, and adverse events were considered, and stratified by specific type and route of medical cannabis without subgroup analyses to confirm systematic differences in effects. The authors only pooled effects when trials reported the same outcome measure, which introduced selection bias. Further, they concluded that medical cannabis did not reduce opioid consumption but failed to report that each trial reporting this outcome required patients to maintain stable opioid doses during the study period (eTable 19).[79-81]

This prior review found similar effects on pain relief in their largest analysis (weighted mean difference −0.44 on a 0-10 visual analogue scale for pain; 95% confidence interval −0.18 to −0.70; 11 trials), which they assigned low certainty evidence due to very serious risk of bias; we did not rate down for risk of bias as subgroup analyses showed no association between risk of bias components and treatment effects. The review authors concluded that the average effect on pain relief was unimportant as it fell below the MID; however, this assumes that all trial patients experience comparable analgesia and fails to consider the distribution around the mean and the proportion of patients who achieve the MID. We converted average effects to the proportion of responders and, based on feedback from our guideline panel which included patient representatives, concluded that some patients may find the modelled proportion of 10% for achieving the MID for pain relief warrants a trial of treatment with medical cannabis.

Strengths and limitations

Strengths of our review include a comprehensive search for eligible RCTs in any language. We engaged a guideline panel of patients and clinical experts to fully contextualise our assessment of the evidence. We used the GRADE approach to appraise the certainty of evidence and converted all significant pooled mean effects to RDs to facilitate interpretation. We found evidence to support the assumptions used for modelling RDs for achieving the MID. We used pre-defined subgroup analyses to explore sources of heterogeneity and assessed the credibility of all potential subgroup effects.

There are some limitations to our review. First, we could not assess long term effects of medical cannabis for chronic pain, because no eligible trial followed patients for more than 5.5 months. Second, over two thirds of the trials included in our review explicitly excluded patients with current or prior substance use disorders or other active mental illness, and the remaining trials did not report if they enrolled patients with mental illness; our findings might not be transferable to this patient population. Third, we present the effect of medical cannabis across different types of chronic pain. Our guideline panel advised it was plausible that cannabis would provide similar effects across chronic pain types, and this was supported by subgroup analyses, which found no systematic difference in treatment effects for neuropathic versus non-neuropathic pain or for chronic cancer versus non-cancer pain. Fourth, high variability among trial effects and the small numbers of trials contributing to some subgroups may have obscured significant subgroup effects. Specifically, PEA and CBD may be less effective than forms of medical cannabis that contain THC (eTable 11 and 12), and medical cannabis may be less effective (or ineffective) for chronic cancer related pain versus chronic non-cancer pain (fig 2, fig 3, eFigure 4, eTable 4). Fifth, although litigation, wage replacement benefits, and veteran status may influence treatment effects, there were insufficient data in the included trials to explore these issues. Sixth, none of our included trials explored inhaled forms of cannabis, and our results may not be generalisable to smoked or vapourised forms of medical cannabis.

Conclusions

In this systematic review of randomised controlled trials, moderate to high certainty evidence shows a small to very small increase in the proportion of people living with chronic pain (cancer and non-cancer) who experience an important improvement in pain relief, physical functioning, and sleep quality with non-inhaled medical cannabis or cannabinoids when compared with placebo, along with several transient adverse side effects. The accompanying *BMJ* Rapid Recommendation provides contextualised guidance based on this body of evidence.

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Contributors: JWB and LW conceived and designed the study. LW, JWB, PJH, CM, YR, YO, CH, BYH, MA, LG, AK, SC, EK, HS, IR and SU acquired the data. LW carried out the statistical analysis. JWB, LW, TA, MAW, FC, and RB interpreted the data. LW and JWB drafted the manuscript. All authors critically revised the article for important intellectual content and gave final approval for the article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

Data sharing: Details of the characteristics of the included studies were shared in the supplementary materials. The study specific data included in the meta-analysis can be obtained from the corresponding author at wangli1@mcmaster.ca.

Transparency: The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We used MAGICapp decision aids (available at www.magicapp.org/) to facilitate conversations between healthcare providers and patients. The MAGICapp decision aids were co-created with people living with chronic pain. We also plan to use social media, the websites of our organizations and pain related associations or societies to disseminate our findings.

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Supplementary material: eTables 1-19, eFigures 1-12, eAppendices 1-4